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☐	L7	photosensitizer adj5 pluronic$	2
☐	L6	drug adj5 triblock$	5
☐	L5	porphyrin adj10 triblock$	0
☐	L4	L3 and liposome	1
☐	L3	photosensitizer adj10 $block$	159
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☐ 1. Document ID: US 6693093 B2

Using default format because multiple data bases are involved.

L4: Entry 1 of 1 File: USPT Feb 17, 2004

US-PAT-NO: 6693093
DOCUMENT-IDENTIFIER: US 6693093 B2

TITLE: Drug delivery systems for photodynamic therapy

DATE-ISSUED: February 17, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Chowdhary; Rubinah K.	Vancouver			CA
Dolphin; David	Vancouver			CA

US-CL-CURRENT: 514/185; 424/486

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWMC | Draw. De

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Terms	Documents
L3 and liposome	1

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L6: Entry 1 of 5 File: USPT Nov 18, 2003

DOCUMENT-IDENTIFIER: US 6649702 B1
TITLE: Stabilization and acoustic activation of polymeric micelles for drug delivery

Brief Summary Text (10):
Polymeric surfactants at various aggregation state have been tested as drug carriers. P-triblock molecules in the uniimeric form (below the critical micelle concentration, CMC) were found to sensitize multi-drug resistant (MDR) cancerous cells. Kabanov and Alakhov [20, 28, 29] have found that there is a-dramatic increase in Daunorubicin and DOX cytotoxic activity toward the multi-drug resistant cell lines while in the presence of 0.01 to 1% of PLURONIC P85 or L61. The efficacy of the drug/P-triblock systems dropped above the CMC. It was concluded that the efficacy of P-triblockdelivery systems was based on the presence of P-triblock unimers.

Brief Summary Text (11):
The drop in the efficacy of drug/P-triblock systems above the CMC may be due to the substantial decrease in the intracellular drug uptake from dense P-triblock micelles. [30-32] The drug incorporated into the micelle core is masked from the external media by the corona composed of PEO chains.

Brief Summary Text (13):
The fundamental difference between using polymeric surfactants below or above the CMC is that below the CMC the enhanced intracellular uptake and enhanced cytotoxicity of the drug delivered with P-triblock unimers is exploited [20, 28, 29, 33], whereas above the CMC, the shielding properties of P-triblock micelles are used to prevent unwanted drug interactions with healthy cells. To ensure drug uptake from (or together with) polymeric micelles at the tumor site, micelle perturbation and cell membrane permeabilization by ultrasound is being proposed [30-32, 34].

Brief Summary Text (27):
To be used as drug carriers, P-triblock micelles require stabilization to prevent degradation caused by significant dilution accompanying IV injection. Three routes of P-triblock micelle stabilization are included in the present invention The first route is direct radical crosslinking of micelles cores which results in micelle stabilization.

Brief Summary Text (30):
The effect of P-triblock concentration in the incubation medium on the intracellular uptake of two anti-cancer drugs was studied. At low P-triblock concentrations, when the drugs were located in the hydrophobic environment, drug uptake was increased, presumably due to the effect of a polymeric surfactant on the permeability of cell membranes. In contrast, when the drugs were encapsulated in the hydrophobic cores of P-triblock micelles, drug uptake by the cells was substantially decreased. This may be used advantageously to prevent undesired drug interactions with normal cells. Ultrasonication enhanced intracellular drug uptake from dense P-triblock micelles. These findings permitted the formulation of a new concept of a localized drug delivery.

Detailed Description Text (31):
Intracellular uptake of DOX and Rb was measured using a fluorescence technique, in which compounds were excited at 488 nm and technical emission spectra were recorded between 510-700 nm. Two sets of samples were studied, one incubated and another sonicated. For the first set (incubated), the cells were incubated at 37.degree. C. with DOX or Rb, which were either dissolved in the RPMI medium (or PBS), or the drugs were solubilized in P-triblock PLURONIC P-105 solutions of various concentrations. For the second set of samples, the cells were sonicated by 70 kHz ultrasound at 379C up to 1 hour in the presence of drug to assess the, effect of ultrasound on the drug uptake from molecular and micellar solutions. After being incubated/sonicated with and without the drug, the cells were spun out, washed twice with cold PBS, and re-suspended in PBS. Sonication power density was maintained at or below 2.4 W/cm.sup.2. No immediate cell death caused by sonication was observed. Sonication in the absence of P-triblock did not, affect cell proliferation. Because drug fluorescence within the cells was substantially quenched, drug uptake was quantified in cell lysates; cells were lysed by incubating them with 1 wt % SDS solution for 1-2 hat 37.degree. C. This process transferred the drug from cellular, components to SDS micelles. Calibration experiments showed a linear dependence of Rb or DOX fluorescence intensity on concentration in 1% SDS solutions in the concentration range of interest. Upon the completion of cell lysis, fluorescence spectra of the lysates were recorded. To quantify the concentration of lysed cells, cell lysates were filtered through 0.2 mm filters, and their optical density was measured by protein absorption at 280 nm (OD 280 nm). Calibration experiments showed a linear dependence of OD 280 nm on the concentration of lysed cells. The fluorescence intensity of lysates was normalized by OD 280 nm. In parallel, the depletion of the drug from the incubation medium was measured by the decrease of supernatants' fluorescence.

Detailed Description Text (86):
Drug Distribution and Release from P-triblock Micelles

Detailed Description Text (88):
Rb was used as a spin- and fluorescent probe to monitor drug distribution in P-triblock micelles and P-gel nanoparticles.

Detailed Description Text (89):
Drug Localization in P-triblock Micelles in the Absence of a Hydrogel

Detailed Description Text (103):
The uptake of either drug was somewhat enhanced at P-triblock concentration of 0.1%, which is below the CMC for the formation of micelles with hydrophobic cores. This is in agreement with Kabanov's data [33] and implies that P-triblock molecules in a unimeric form or in loose aggregates enhance the permeability of cell membranes toward the drugs (FIG. 17) [31].

Detailed Description Text (104):
Drug sequestering in P-triblock PLURONIC P-105 micelles with hydrophobic cores caused substantial decrease in drug uptake by HL-60 cells, indicating that dense micelles inhibited drug interaction with the cells (FIG. 17).

Detailed Description Text (105):
Acoustically Activated Drug Release from Unstabilized and Stabilized P-triblock Micelles Under Continuous Wave Ultrasound

Detailed Description Text (113):
A custom ultrasonic exposure chamber with real-time fluorescence detection was used to measure acoustically-triggered drug release from P-triblock PLURONIC P-105 micelles under continuous wave (CW) or pulsed ultrasound in the frequency range of 20 kHz to 90 kHz. The measurements were based on the decrease in fluorescence intensity when drug was transferred from the micelle core to the aqueous

environment. Two fluorescent drugs were used: doxorubicin (DOX) and its paramagnetic analogue, ruboxyl (Rb). P-triblock PLURONIC P-105 at various concentrations in aqueous solutions was used as a micelle-forming polymer. Drug release was highest at 20 kHz ultrasound and dropped with increasing ultrasonic frequency despite much higher power densities. These data suggest an important role of transient cavitation in drug release. The release of DOX was higher than that of Rb due to stronger interaction and deeper insertion of Rb into the core of the micelles. Drug release was higher at lower P-triblock concentrations, which presumably results from higher local drug concentrations in the core of P-triblock micelles when the number of micelles is low. At constant frequency, drug release increased with increasing power density. At constant power density and for pulse duration longer than 0.1 s, peak release under pulsed ultrasound was the same as stationary release under CW ultrasound. Released drug was quickly re-encapsulated between the pulses of ultrasound, which suggests that upon leaving the sonicated volume, the non-extravasated and non-internalized drug would circulate in the encapsulated form, thus preventing unwanted drug interactions with normal tissues.

Detailed Description Text (119):
The experimental procedure is described below. First, fluorescence intensity of drug in phosphate buffered saline, PBS (F.sub.PBS) was measured; then, without any changes in the experimental setup, the PBS solution was carefully removed and replaced with the drug solution in P-triblock micelles. In all experiments, Rb concentration was 20 .mu.g/ml and DOX concentration was 40 .mu.g/ml. The base fluorescence of the micellar solution (F.sub.mic) was measured, after which CW or pulsed ultrasound was turned on. During the "ultrasound on" phase, fluorescence dropped as shown in FIG. 19 due to drug release from the hydrophobic core of micelles into the aqueous environment.

Detailed Description Text (126):
Drug Encapsulation in P-triblock Micelles

Detailed Description Text (137):
Examples of the release profiles of drugs from 10% P-triblock micelles are shown in FIG. 20 for Rb at 47-kHz sonication and in FIG. 21 for DOX at 20-kHz sonication respectively; both CW and pulsed ultrasound with various duty cycles were explored.

Detailed Description Text (138):
The drop in fluorescence intensity during the "ultrasound on" phase indicates drug release from the hydrophobic environment of P-triblock micelle cores into the aqueous environment, which may result either from ultrasound-induced drug diffusion out of micelles or from micelle degradation under sonication, as discussed below.

Detailed Description Text (148):
Not much difference was observed between Rb (or DOX) release from 10% and 1% P-triblock micelles; however, significantly higher release of Rb and DOX was observed from 0.1% solutions at all frequencies and power densities studied. For Rb, release was between 11 to 13% from 0.1% solution vs. 5.5% from 10% solution (at 67 kHz and 2.8 W/cm.sup.2 power density). Data for DOX at 20 kHz are presented in FIG. 22 (note that measurements of drug release from P-triblock solutions of low concentrations are slightly less accurate than those for 10% or 1% solutions because of decreased differences between drug fluorescence in P-triblock and PBS). Higher drug release from P-triblock solutions of lower concentrations may be due to higher local drug concentration in the core of P-triblock micelles when the number of micelles is low, i.e. at P-triblock concentrations only slightly above the corresponding CMC (which is 0.03% for P-105 at 37.degree. C., based on data presented in [84]). This is corroborated by the finding that for the same P-triblock concentration of 10%, drug release indeed increased with increasing initial concentration of drug in the solution. At a concentration of 40 .mu.g/ml, DOX release was 10%.+-.1% (mean and s.d.), while at a concentration of 30 .mu.g/ml,

the release was 5.5%.+-.1% (at 67 kHz and 2.8 W/cm.sup.2 power density). The lower drug release at the lower drug concentration could be attributed to a higher ratio of PPO to DOX in the hydrophobic core of P-triblock micelles, which favors hydrophobic interaction. It is postulated that increased hydrophobic interaction reduces percentage of drug that can be released from micelle core upon the application of ultrasound. This is confirmed by the above mentioned lower release of Rb in comparison to DOX. At higher local drug concentrations in micelle cores, drug/PPO hydrophobic interactions are replaced by weaker drug/drug interactions, which facilitates drug release.

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L6: Entry 4 of 5 File: USPT Dec 30, 1997

DOCUMENT-IDENTIFIER: US 5702717 A
TITLE: Thermosensitive biodegradable polymers based on poly(ether-ester)block copolymers

Brief Summary Text (69):
Because of the surfactant-like properties of these block copolymer systems, the diluted polymer solution forms a milky emulsion when the polymers loses its solubility in water. This self-emulsifying system is also of great interest because moderately hydrophobic drugs can be dissolved by the surface active triblock copolymers disclosed herein and then can be incorporated into emulsions (or suspensions) formed spontaneously at body temperature. The triblock copolymers can also be considered as degradable nonionic surfactants which are superior in function to the non-degradable Pluronic.TM. system. Certain peptides and proteins will also be adsorbed onto or entrapped into this system and formulated as a new type of controlled release delivery system. The drugs can be released slowly with degradation of the particles. Eventually, no further microencapsulating process, which are time-consuming and mostly requires organic solvents, is needed. The poly (ether-ester) block copolymers described in the present invention has temperature-sensitivity and has great potential for the development of the self-gelling or self-emulsifying, biodegradable depot system which can be injected extravascularly and release the incorporated or entrapped drug in a sustained manner.

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L6: Entry 5 of 5 File: EPAB Apr 1, 1999

DOCUMENT-IDENTIFIER: WO 9915151 A1
TITLE: ACOUSTICALLY ACTIVATED LOCALIZED DRUG DELIVERY

Abstract Text (1):
CHG DATE=19990905 STATUS=O>A method for administering a drug to a selected site in a patient includes the steps of (a) administering a composition including a micellar drug carrier having a hydrophobic core and an effective amount of the drug disposed in the hydrophobic core; and (b) applying ultrasonic energy to the selected site such that the drug is released from the hydrophobic core to the selected site. Preferably, the drug carrier is a triblock copolymer, such as a poly (ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) block copolymer having a molecular weight of about 6500. The drug is preferably an antineoplastic agent such as doxorubicin.

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☐ 1. Document ID: US 6649702 B1

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L6: Entry 1 of 5 File: USPT Nov 18, 2003

US-PAT-NO: 6649702
DOCUMENT-IDENTIFIER: US 6649702 B1

TITLE: Stabilization and acoustic activation of polymeric micelles for drug delivery

DATE-ISSUED: November 18, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Rapoport; Natalya	Sandy	UT		
Pitt; William G.	Orem	UT		

US-CL-CURRENT: 525/299; 424/486, 424/487, 424/489, 523/201, 524/504, 524/505, 525/280, 525/284, 525/327.3

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

☐ 2. Document ID: US 6592899 B2

L6: Entry 2 of 5 File: USPT Jul 15, 2003

US-PAT-NO: 6592899
DOCUMENT-IDENTIFIER: US 6592899 B2

TITLE: PLA/PLGA oligomers combined with block copolymers for enhancing solubility of a drug in water

DATE-ISSUED: July 15, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Fowers; Kirk Dee	Layton	UT		
Zentner; Gaylen M.	Salt Lake City	UT		
Shih; Chung	Sandy	UT		
Piao; Ai-Zhi	Salt Lake City	UT		

US-CL-CURRENT: 424/486; 424/426, 424/430, 424/434, 424/444, 424/449, 424/484, 525/411, 525/413, 525/415

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWMC | Draw De

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☐ 3. Document ID: US 6545097 B2

L6: Entry 3 of 5 File: USPT Apr 8, 2003

US-PAT-NO: 6545097
DOCUMENT-IDENTIFIER: US 6545097 B2
**** See image for Certificate of Correction ****

TITLE: Drug delivery compositions and medical devices containing block copolymer

DATE-ISSUED: April 8, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Pinchuk; Leonard	Miami	FL		
Nott; Sepideh	Weston	MA		
Schwarz; Marlene	Newton	MA		
Kamath; Kalpana	Natick	MA		

US-CL-CURRENT: 525/240; 424/423, 424/501, 525/221, 525/242

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWMC | Draw De

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☐ 4. Document ID: US 5702717 A

L6: Entry 4 of 5 File: USPT Dec 30, 1997

US-PAT-NO: 5702717
DOCUMENT-IDENTIFIER: US 5702717 A

TITLE: Thermosensitive biodegradable polymers based on poly(ether-ester)block copolymers

DATE-ISSUED: December 30, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Cha; Younsik	Salt Lake City	UT		
Choi; Young Kweon	Salt Lake City	UT		
Bae; You Han	Kwangju			KR

US-CL-CURRENT: 424/425; 424/424, 424/426, 424/486, 424/501, 604/891.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWMC | Draw De

☐ 5. Document ID: WO 9915151 A1

L6: Entry 5 of 5 File: EPAB Apr 1, 1999

PUB-NO: WO009915151A1
DOCUMENT-IDENTIFIER: WO 9915151 A1
TITLE: ACOUSTICALLY ACTIVATED LOCALIZED DRUG DELIVERY

PUBN-DATE: April 1, 1999

INVENTOR-INFORMATION:

NAME	COUNTRY
RAPOPORT, NATALYA	US
PITT, WILLIAM G	US

INT-CL (IPC): A61 K 9/10; A61 K 47/32
EUR-CL (EPC): A61K009/107; A61K009/00

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWMC | Draw De

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drug adj5 triblock$	5

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L7: Entry 2 of 2 File: USPT Nov 14, 1978

DOCUMENT-IDENTIFIER: US 4125503 A
TITLE: Ultraviolet curing emulsion systems

Detailed Description Text (2):
50 parts of an epoxy diacrylate made by reacting hydroxy ethyl acrylate with a diglycidyl ether of bisphenol A having a molecular weight of about 390 is dissolved in 50 parts of butyl carbamoyl ethyl acrylate, and the solution is mixed with 5 parts of benzophenone photosensitizer and 10 parts of Pluronic F 127 emulsifier. This mixture is subjected to high speed agitation and 100 parts of deionized water is added slowly to produce an emulsion having an average particle size of less than about 1 micron.

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L9: Entry 11 of 19 File: USPT Jul 10, 2001

DOCUMENT-IDENTIFIER: US 6258378 B1
TITLE: Delivery of biologically active substance to target sites in the body of patients

Brief Summary Text (31):
Emulsifiyng or surfactant agent may also be incorporated in the liposomes or used for liposome preparation, such as Pluronics.RTM., Poloxamer.RTM., Span.RTM., Brig.RTM., Tweens.RTM., Triton-X.RTM.; fluorinated surfactants such as Zonyl.RTM..

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